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Application No. 10/020,331

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First Named Inventor: Michael T Milbocker

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Commissioner for Patents
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DECLARATION UNDER RULE 132

Michael T. Milbocker, Ph.D., declares as follows:

1. I am the inventor in the above referenced patent application.

2. During the development of the prepolymer used as an adhesive in the application having serial no. 10/020,331, formulations were synthesized of greater and lesser proportions of propylene glycol (or propylene oxide; PO) subunits than the range currently claimed of 10% to 30% propylene glycol subunits as being suitable as a tissue adhesive.

3. Experiments described in the specification of the application, for example in 1 through 7, are representative of compositions useable as tissue adhesives. Other experiments, not cited in the Application, were used to estimate the useable range of compositions.

3. As a limiting case of low propylene glycol content, pure polyethylene glycol (100% EO, ethylene oxide; 0% PO) was endcapped and trimerized with TDI (toluene di-isocyanate) and TMP (trimethylol propane), essentially as described in the application, to yield a prepolymer which polymerizes when mixed with water. This prepolymer was applied to fresh bovine tissue. It readily bonded to the tissue, but swelled to greater than 300% when placed in water. The swelling resulted in a bond that was weak, and tissue bonded together using this preparation easily separated when a tension force greater than 0.5 lb/sq.in. was applied perpendicular to the bond plane.

4. As a limiting case of high propylene glycol content, pure diols of polyethylene glycol and of polypropylene glycol were mixed in equal proportion (50:50) by weight. (This corresponds to about 42% propylene oxide subunits by number.) TDI was added to chain extend the mixture to approximately 1000 D and subsequently trimerized with TMP. The OH groups on the ends of the chain extended diols (1000 D) were already functionalized with TDI and readily reacted with the TMP to form trimers. This composition when applied to fresh bovine tissue was resistant to wetting the tissue surface. The composition polymerized without making bonds to the tissue, and once fully polymerized could easily be washed from the tissue surface with minimal force.

5. In later experiments, including examples 6 and 7, a 25:75 PO:EO ratio polyol material, available commercially as "Voranol", has been found to be somewhat better in terms of strength. This is currently the preferred embodiment. Conveniently, it is already trimeric, and so does not require the added step of trimerization.

6. I concluded, before the submission of the application in 2001, that an upper and lower range of PO content for synthesizing an effective tissue adhesive existed, and demonstrated that an effective tissue adhesive, having a removal force of above 4.5 lb per square in., was synthesized with a number ratio of 20:80 polypropylene glycol to polyethylene glycol. Based on the experiments cited above, it was believed that the range

for an effective tissue adhesive requires at least 5% PO units by number, preferably at least about 10% for good strength, and not above about 30%.

7. The above experiments were the basis for the declarations found in paragraphs 45 - 48 of the application as published.

8. In the four years of experimentation that have followed the initial submission, I continue to find that having a minimum proportion of PO units in a tissue adhesive is necessary to minimize swelling and retain strength in the bond. I also continue to find that there is an upper limit of PO concentration in the diol polymer, somewhat variable depending on the ratio of isocyanate residues to total polyol, but approximately 30% by number (or about 36% by weight), above which the adhesive does not adhere well to tissue.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 USC 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Michael Milbocker 2-13-06

Michael T. Milbocker date

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